Miller receives Target ALS award to study therapy for Lou Gehrig's disease

By Eddy Ball

In January, NIEHS lead investigator David Miller, Ph.D., received a 3-year grant to improve therapeutic drug delivery for treating amyotrophic lateral sclerosis (ALS), the fatal neurodegenerative condition also known as Lou Gehrig's disease.

The grant from Target ALS *(http://news.columbia.edu/research/3062)* will provide Miller with $138,770 to support research into how the central nervous system (CNS) becomes drug resistant during the progression of ALS. He and his group will also work to create a strategy for delivering therapeutic drugs to where they need to be, across the blood-brain and blood-spinal cord barriers that protect the CNS from environmental and other potentially damaging exposures.

"This is a wonderful opportunity for our group to translate our years of research into regulation of chemical transport across the tissue barriers that protect the CNS, to improve treatment for this terrible disease," said Miller. "As we've learned, the body doesn't discriminate very well between harmful chemicals and therapeutic drugs, and this protective mechanism contributes to the poor success rate of CNS drug candidates."

Experiments will focus initially on enhancing the effectiveness of riluzole, the only drug currently approved by the U.S. Food and Drug Administration for treatment of ALS. Because of the tissue barriers to delivery, riluzole typically prolongs survival by only around 2 months, about as long as it took for the ALS Association Ice Bucket Challenge to go viral last summer.

"Basically, we hope to be able to stop the disease-driven and selective tightening of the brain's barriers to certain drugs," he explained. "Doing this may improve therapy with current and novel therapeutics." (Photo courtesy of Steve McCaw)

Breaking down silos in ALS research and fostering collaborations

Established in 2013, Target ALS is promoting a systemized approach to screening ALS therapies and generating a pipeline of candidate therapeutic targets for drug development. Its goal is to provide a central organization for scientists, academics, and health care and business professionals to share ideas, progress, and discoveries.

Miller will be part of consortium that includes neurobiologists Piera Pasinelli, Ph.D., *(http://www.jefferson.edu/university/jmc/departments/neuroscience/faculty /faculty/pasinelli.html)* and Davide Trotti, Ph.D., *(http://www.jefferson.edu/university/farber_institute/weinberg_als_unit/ faculty/trotti.html)* founding co-directors of the Thomas Jefferson University Weinberg Unit for ALS Research *(http://www.jefferson.edu/university/farber_institute/weinberg_als_unit.html)* in Philadelphia. The team will advance previous work on transport proteins, which function as drug efflux pumps within the tissue barriers and serve as selective gatekeepers for the central nervous system.

Pasinelli and Trotti established the Weinberg Unit in 2006 as part of their long-time collaboration on ALS and pharmacoresistance. Pasinelli, Trotti, and Miller have co-authored two studies, including a 2014 review (http://www.ncbi.nlm.nih.gov/pubmed/25175835) published in Brain Research. (Photo courtesy of Thomas Jefferson University)

The aims of Miller's part of the project are to use a mouse model of ALS to determine the critical period during disease progression when transporter activity and expression increases; map the signals within the neurovascular unit responsible for those increases; and devise a strategy to block signaling, prevent transporter upregulation, and increase delivery of riluzole and other therapeutics to the CNS.